AMERICAN SOCIETY FOR CLINICAL PHARMACOLOGY AND THERAPEUTICS

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ONE-HUNDREDTH ANNUAL MEETING: MARRIOTT RIVERCENTER, SAN ANTONIO, TEXAS – MARCH 18-20, 1999

August 12, 1998

Docket Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sir/Madam:

I am pleased to submit a statement on behalf of the American Society for Clinical Pharmacology and Therapeutics (ASCPT) which form the basis of the Society's presentation that will be made by D. Craig Brater, MD at the CDER Stakeholders meeting on August 17, 1998. Dr. Brater is a former President of ASCPT and Chair of the Department of Medicine at the University of Indiana.

Sincerely,

David A. Flockhart, MD, PhD
Chairperson, Government Affairs Committee

cc: Susan H. Carey, FDA
Denise Gavetti, ASCPT

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Docket No. 98N-0339

Statement of the American Society for Clinical Pharmacology and Therapeutics
In Response to the Food and Drug Administration's
Request for Comments

The American Society for Clinical Pharmacology and Therapeutics is pleased to be able to respond to the Agency's call for comment (Federal Register: July 24, 1998 (Volume 63, Number 142), and the letter to CDER Stakeholders from Janet Woodcock, Director, CDER, July 21, 1998). The Society, founded in 1900, is the largest and oldest medical society dedicated solely to therapeutics. The Society has long been at the forefront of drug development and research to improve therapeutics. The over 2,100 members of the Society represent many of the physicians and scientists who have participated in the development or testing of the drugs that are prescribed by the nation's physicians.

We have organized our comments according to three general areas:

#1 Safety of Marketed Products
#2 Maximization of Information for Consumers
#3 Scientific Expertise & Infrastructure for FDA

#1. **Safety of Marketed Products**. *Described in Federal Register (FR) Objective "(3) implementing inspection and post-market monitoring provisions of the act"; Question" 3. How can FDA work with its partners to ensure that products—both domestic and foreign-produced and marketed by the regulated industry are of high quality and provide necessary consumer protection; and how can FDA best establish and sustain an effective, timely, and science-based post-marketing surveillance system for reporting, monitoring, evaluating, and correcting problems associated with use/consumption of FDA-regulated products?"; Letter to CDER Stakeholders question" 4. Surveillance and Adverse Event Reporting - Adverse events thought to be associated with medicines were recently reported to be the sixth largest cause of death in the United States. CDER has recently modernized its reporting system. What else needs to be done to detect, analyze, communicate, and respond to the causes of death and injury from medicines?"*

a. **Role of Centers for Education and Research in Therapeutics (CERTs), Authorized in FDAMA**. The American public has been lulled into a sense of security by a strong and efficient FDA and the billions of dollars spent to promote new therapies. This security has been challenged by recent studies that suggest that as many as 116,000 deaths per year may result from adverse drug reactions, which would therefore constitute the sixth leading cause of death in this country (Bates DW: Drugs and adverse drug reactions. How worried should we be? JAMA 279:1216-1217, 1998.) While the merits of the precise data are debated, we all agree that an unacceptable number of fatalities occur. Physicians and pharmacists must increase their efforts to be fully familiar with FDA-approved drug labels and to use caution and careful monitoring, especially when drugs are used outside of labeled

instructions. In addition, the public must become aware that the FDA judges new drugs to be "relatively safe" when used as intended, not "perfectly safe under all possible circumstances". The public must recognize that there could be unforeseen interactions between a new drug and other medications that they might be taking. In this era of managed care, when physicians and pharmacists have a diminishing window of time to communicate with patients, the burden falls increasingly on patients to be well informed about all of their medications and to be active participants in the therapeutic experiment that is inherently part of every prescription.

Properly established and adequately funded, a system of educational and research centers would provide the needed data and an unbiased voice of moderation informing patients, nurses, pharmacists and physicians about medicines. The research conducted would provide data to assist in identifying new drug toxicities, drug interactions, and factors essential for the optimal use of medications in children, the very elderly and other unstudied populations. The centers would examine important issues such as ethnic and gender differences in drug response and drug safety. They would also conduct educational programs to convey this valuable information to the public and all healthcare providers.

b. **Increased Staff for Drug Safety in the Agency**. To improve the post-marketing surveillance of new drugs, the recommendations of a 1980 Congressional Commission on Prescription Drug Use should be acted on. This Commission called for creation of a comprehensive drug safety program. Even though the FDA has acted appropriately on the problems uncovered with new drugs, they could have acted even more quickly had they been given the needed resources. As called for in 1980, there is a need to strengthen the FDA's MedWatch voluntary reporting system by providing additional trained physicians and other scientists to review and conduct in-depth analyses of the hundreds of thousands of adverse event reports that are received on over 5000 regulated drugs and devices. The Agency should provide adequate staff and resources for the in-depth analysis of the MedWatch reports using hypotheses based upon the pharmacology, clinical pharmacology and toxicology of drugs. For example, there are approximately 40 marketed drugs with the known potential to cause life-threatening ventricular arrhythmias. For many of these, known predisposing factors such as female gender should be incorporated into any systematic surveillance of the MedWatch Database. However, this requires a multidisciplinary approach to planning such analyses and would optimally involve a team of pharmacologists, clinical pharmacologists, epidemiologists and regulatory scientists. Additionally the FDA should develop systems similar to those employed in European countries to prospectively gather data on the outcome of patients treated with newly marketed drugs.

c. **Independence of Post-marketing Safety Decisions From the Medical Review Process**. ASCPT suggests that FDA consider adopting a procedure for the final assessment of post-marketing safety to be made by FDA scientists who are independent of the review and approval process because of the potential for a perceived or real bias on the part of NDA reviewers.

d. **Regulatory Research on Safety Factors**. ASCPT encourages FDA to conduct regulatory research, into the importance of the following patient factors affecting drug

safety: ethnicity, gender, risk in the very elderly and the very young, and those taking multiple medications.

e. **Risk/benefit Assessment of Life-style Modifying Drugs**. FDA's risk/benefit analysis and post-marketing safety assessments of drugs used for life-style modification/improvement should be re-examined. The current drug safety surveillance system is designed for drugs that have an acceptable risk benefit ratio in which the benefit is effective treatment of a disease or disorder. This may be inappropriate for drugs that are being developed for lifestyle modification or cosmetic purposes. The FDA should reevaluate the entire drug approval and drug safety system for drugs that have the intended or high potential for use in non-therapeutic applications.

(#2.) **Maximization of Information for Consumers**. *FR Objective "(2) maximizing the availability and clarity of information for consumers and patients concerning new products"; FR Question "2. How can the agency maximize the availability and clarity of information concerning new products?"; Letter to CDER Stakeholders question "3. Drug Information. - CDER is an authoritative and independent source of drug information. How can we assure that health professionals and consumers get the information they need about drugs? What methods of communication would be most effective in getting additional information about drugs to health professionals and consumers?"*

a. **Modernization of Drug Labels**. Modernization of access to FDA reviewed and approved drug information using state-of-the-art electronic and internet communications technology should be given high priority. Currently, the traditional, single format, infrequently updated, paper print label, is expected to serve the needs of all potential users, including physicians, pharmacists, clinical pharmacologists, nurses, patients and their families, regulators, lawyers, medical researchers, et al. ASCPT believes that the maximum permissible source scientific data underlying label conclusions should be available to consumers who need them. In view of advances in information technology (as already demonstrated by FDA's impressive and highly useful web page), ASCPT urges FDA to begin the transition towards a frequently updated, internet based drug label database that can be queried by any user, allowing user-specified information to be extracted in a format that best suits the user's needs.

b. **Assuring Availability of Objective Drug Information**. The availability of quality information about medications that is available to prescribers and to the public is rapidly decreasing with the disappearance of *AMA Drug Evaluations* and the uncertain future of *USP Drug Information*. Much of what remains are the FDA/Industry negotiated product label and the educational and marketing activities of specific companies. This means that a critical gap in provision of quality objective drug information is widening at a time when drug prescribing and usage is increasingly documented to be suboptimal. Reports of patient harm due to inappropriate prescribing must be considered a warning and call to action. ASCPT believes that CDER has the responsibility and the opportunity to take the lead in correcting this information gap in the following ways:

1. By collaborative activity with USP to rescue and enhance the information reservoir contained in USP-DI/AMA-DE
2. By vigorous support for the educational component of the Centers for Education and Research in Therapeutics (CERTs).

   Role of CERTs in Maximization of Information for Consumers. The FDA does not currently have an effective mechanism to communicate its wealth of information on the optimal use of the medications that it regulates. However, the creation of CERTs, authorized in FDAMA, provides an excellent avenue for the agency to convey unbiased independent messages about the optimal use of medications. Working with the CERTs the Agency could participate in an educational program that would inform the public of general public service messages, e.g. "Do not take medications that might interact", "Request counseling from your physician and your pharmacist", etc. Further, Agency scientists could participate in the educational programs of CERTs. Examples would be to serve as guest lecturers in medical schools and by collaborating in the creation of educational tools that promote rational drug prescribing for physicians in training would be a valuable addition to the medical education

3. By continuing participation in professional societies committed to education in rational therapeutics (e.g. ASCPT and other societies).

#3 **Scientific Expertise and Infrastructure for FDA**. *Federal Register Objective (FR)"(4) assuring access to the scientific and technical expertise needed to carry out FDA's obligations", FR Question 4. What approach should FDA use to assure an appropriate scientific infrastructure, with continued access to the scientific and technical expertise needed to meet its statutory obligations and strengthen its science-based decision making process?"*

I. RECRUITMENT OF QUALIFIED SCIENTIFIC STAFF, MENTORING, RETENTION, ADVANCEMENT AND RENEWAL.

a. **Recruitment and Mentoring** of scientists qualified to establish appropriate scientific and medical standards, and to critically review IND, NDA, and post-marketing data on safety and efficacy of drugs should continue to be a high priority goal of CDER. ASCPT believes that education and experience in drug evaluation sciences, especially clinical pharmacology, clinical investigation, and biopharmaceutics are critical professional backgrounds to seek in candidate employees who will play roles in reviews of safety and efficacy data in INDs, NDAs, and post-marketing surveillance programs. It is important to assure personal mentoring and close supervision by experienced FDA staff of new recruits as well as veteran staff assigned new duties.

b. **Balancing Retention and Recruitment**. In order to ensure that FDA standards and regulatory reviews keep up with the scientific state of the art, a balance between retention and advancement of a veteran FDA scientific staff and influx of qualified new scientists should be sought. This is especially critical at Division and Office leadership levels, where maintenance and renewal of state of the art scientific leadership is critical for the FDA to be able to competently review and/or guide scientific advances in drug development.

c. **Job Advertising**. A vigorous program of promotion and advertising of scientific job openings at FDA should be established, including involvement of professional societies such as ASCPT and AAPS. Consideration should be given to a novel employment program that provides time limited (2-5 year) employment of academic scientists that would enable opportunity for the 'best and brightest' scientists to contribute to the critical public safety mission of the FDA.

d. **Tenure in Key Leadership Positions**. In order to further ensure ongoing institutional renewal of vigorous, scientific leadership at the state-of-the-art, a program of time-limited tenure of Division and Office Directors should be instituted with reappointment based on a national search with a competitive selection process. A sabbatical program for career FDA scientific leaders (Division and Office director levels) should be established to enable hands-on renewal of scientific knowledge and skills at the state-of-the-art.

e. **National Search Committees**. Since renewal and invigoration of scientific leadership at the Division and Office leadership levels is especially critical to "assure an appropriate scientific infrastructure, with continued access to the scientific and technical expertise needed to meet its statutory obligations and strengthen its science-based decision making process", a formal National Search Committee process should be established, in which National Search Committees comprise both internal FDA staff and external scientists employed in academia, and other parts of government.

II. CONTINUING EDUCATION

a. **Maintaining Knowledge & Skills**. Acquisition and maintenance by career scientific FDA staff of advanced, up-to-date knowledge and skills in drug evaluation sciences should be ensured via augmentation or creation of the following programs:

1. FDA Staff College. ASCPT supports establishment of a cross-center FDA Staff College to achieve continuing education goals for all FDA medical product reviewers. Augmentation of CDER's Division of Training and Development (Office of Training and Communication) curricula is advised to provide remedial, advanced, and cutting-edge scientific course offerings, including topics in clinical pharmacology, clinical investigation, and drug development science that are essential for reviewers of drug efficacy and safety data in INDs, NDAs, and post-marketing surveillance programs.
2. Continuing Education Credits. A FDA monitored employee career development program that requires continuing scientific education credits through a variety of education programs, including participation in FDA Staff College scientific courses, external scientific courses, conferences, workshops, and research.
3. Professional Development Activities. Continuation and augmentation of scientific staff involvement in professional development activities (up to 20% time) such as

FDA relevant scientific research and clinical practice activities. This could be conducted via local and national collaborations with high quality academic institutions, including the NIH.

4. Sabbatical Program. Sabbatical program that enables career FDA scientists to spend one month to two years in an external research or educational program of value to the scientist's future role in FDA.

b. **Involvement in the Collaboration on Drug Development Improvement**. As an avenue for both continuing education and personal contribution, FDA scientific staff are encouraged to be involved in the Collaboration on Drug Development Improvement (CDDI). CDDI is a project designed to advance the drug development process for pharmaceuticals, through ICH-like working parties that contribute to development of guidance documents for pharmaceutical scientists on efficient, scientifically sound approaches. The collaboration comprises FDA (CDER, CBER), PhRMA, BIO, the Georgetown University Center for Drug Development Science, and the MIT Sloan School of Management.

III. SCIENTIFIC CULTURE AT FDA

Acknowledging that FDA relies upon the application of scientific principles and approaches to assure the safety, effectiveness and timely access to therapeutic agents, ASCPT supports and encourages the following aspects of the scientific culture at FDA:

a. **Regulatory Research.** Augmentation of internal FDA and contract scientific research that is relevant to FDA's mission, i.e. applied regulatory research necessary to support regulatory policy as reflected in Agency guidances. This research requires a sophisticated understanding of scientific methods and approaches, including approaches in molecular biology, pharmacometrics, clinical pharmacology, biopharmaceutics, and statistics, and ASCPT believes that it should be given a high priority in the development of a cutting-edge scientific culture at the Agency.

   Such regulatory research should have direct relevance to the development of regulatory policy. Establishing regulatory policy is a resource intensive effort that involves developing public standards for information and assessment of this information. Public standard-setting requires the most up-to-date understanding of science and technology. This allows the Agency to optimize the information required to establish the efficacy, safety, and quality of a new drug. This information should arise from sensitive and specific studies that assure optimum information is generated, yet unnecessary or inappropriate regulatory burdens are not imposed. Defense of a regulatory approach occurs in the public arena and requires public access to the best information possible and to sound interpretation of this information. Participation by agency review staff in the generation of this essential information enhances their skills and commitment, and provides opportunities for professional development.

b. **FDA Staff Involvement in CERTs**. An important component of any retention program for FDA scientists should include opportunities for active participation in the FDA's collaborative regulatory research programs. FDAMA authorized the creation

of Centers for Research and Education in Therapeutics (CERTs). The funding and activation of this program should be encouraged because it will create a new and exciting opportunity for scientists at the Agency to collaborate in the conduct of important research that will serve consumers in more informed use of medications and the Agency in fulfilling its regulatory responsibility. Agency scientists should be encouraged to use their professional development time to participate in the research activities of the CERTs.

c. **Continuing Scientific Education** as described in II above.
d. **Participation of FDA Scientists in Professional Scientific Society Activities** (e.g. ASCPT, AAPS, ACCP, and medical subspecialty societies)
e. **FDA Staff Teaching** of FDA scientific applications internally and in academia, professional scientific societies, and public forums.
f. **FDA Staff Involvement in Internal FDA Scientific and Academic Activities** such as faculty participation in FDA electronic journal publications, FDA Staff College activities, CDER Seminars and Scientific Rounds, scholarly debates on application of scientific principles to FDA standards and reviews of INDs and NDAs.
g. **FDA Scientific Staff Involvement in the Collaboration on Drug Development Improvement** (see II.c., above).

IV. ACCESS TO SCIENTIFIC AND TECHNICAL EXPERTISE

Recognizing that in addition to I-III above, FDA must have "continued access to the scientific and technical expertise needed to meet its statutory obligations and strengthen its science-based decision making process", ASCPT supports the Agency in its efforts to augment the solicitation and receipt of advice and input from external consultants. ASCPT would like to offer the following, specific recommendations:

a. **Contributions to FDA Guidances**. A special opportunity for useful external contributions exists in the area of good guidance practices. FDA's Good Guidance Practices document (FR February 18, 1997) states that FDA may solicit or accept early input on the need for a new or revised guidance from individual non-governmental groups such as consumer groups, trade associations, patient groups, and public interest groups. Interactions to make this input possible can occur in meetings with these various parties or FDA may also hold meetings and workshops with each interested party on the development or revision of specific guidances. Building on past interactions of this nature (e.g. analgesics guidelines development supported by ASCPT), ASCPT welcomes this opportunity and looks forward to further opportunities to provide expert science advice on specific topics of interest to FDA and to the Society.
b. **Recruitment of Advisory Committee Members**. Recruitment and selection of scientific advisory committee members should be undertaken with the same level of priority as that described in I. above. Chairpersons of FDA scientific advisory committees should be specifically recruited to this position, with recognized qualifications in drug development and/or regulatory sciences.
c. **Advisory Committee Expertise in Clinical Pharmacology and Biopharmaceutical Activities**. ASCPT believes that education and experience in drug evaluation

sciences, especially clinical pharmacology, clinical investigation, and biopharmaceutics are critical professional backgrounds to seek in candidate advisory committee members. Each advisory committee should have at least one qualified clinical pharmacologist nominated by ASCPT and one qualified biopharmaceutical scientist nominated by AAPS.

d. **Independency of Advisory Committees**. While FDA scientific advisory committees should remain "advisory to FDA", their procedures should be given more autonomy and independence from FDA staff influences, so that their deliberations may be viewed as objective assessments, based on the facts and scientific merits of all information brought before them.

e. **Responsibility for Quality Control of Advisory Committees**. Oversight, responsibility and quality control of scientific advisory committees should reside at the Center Director level.